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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/582,482	10/13/2000	Richard Derosé	PH 97089	3435

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CONNOLLY BOVE LODGE & HUTZ, LLP  
1220 N MARKET STREET  
P O BOX 2207  
WILMINGTON, DE 19899

EXAMINER

MARX, IRENE

ART UNIT	PAPER NUMBER
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1651

DATE MAILED: 02/05/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

# Office Action Summary

Application No.  
09/582,482

Applicant(s)  
Derose et al.

Examiner  
Irene Marx

Art Unit  
1651



--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

## Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☒ Responsive to communication(s) filed on Oct 28, 2002
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

## Disposition of Claims

- 4) ☒ Claim(s) 1-8, 12, and 13 is/are pending in the application.
- 4a) Of the above, claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-8, 12, and 13 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claims \_\_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.  
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

## Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) ☐ All b) ☐ Some\* c) ☐ None of:  
1. ☐ Certified copies of the priority documents have been received.  
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_  
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).  
\*See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).  
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

## Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). \_\_\_\_\_ 6) ☐ Other:

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/28/02 has been entered.

Claims 1-8 and 12-13 are being considered on the merits.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-8 and 12-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is vague, indefinite and confusing in requiring the bioconversion of 4-hydroxypyruvate enzymatically to 4-hydroxyphenylacetate with a suitable enzyme. This bioconversion appears unlikely, since it requires addition of a phenyl group. Also a source of acetate appears to be required. In addition the abbreviation "HPP" is incorrect for 4-hydroxypyruvate. Clarification and correction are required. No new matter may be added.

Claim 1 is confusing in the recitation of "first suitable enzyme" and "second suitable enzyme", since dependent claim 2 suggests a "suitable HPP-oxidase" and claim 4, a "suitable HPA-hydroxylase". It is unclear whether or not the enzymes of claim 1 are the same or different from those of claims 2 and 4. If they are the same, the respective limitation should be incorporated into claim 1. See also page 2, lines 25 et seq. of the Specification, wherein it is stated that the first reaction is catalyzed by a "suitable HPP-oxidase" and the second with a "suitable HPA-hydroxylase". It is noted that an inhibitor of a 4-hydroxyphenylpyruvate dioxygenase (HPPD) has to be present. This strongly suggests that this enzyme or an enzyme closely related thereto is used in the bioconversion.

Claims 2 and 4 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim 1 is vague and indefinite in the recitation of “in the presence of a... HPPD inhibitor”, since it is doubted that in the “presence” of large amounts of any inhibitor the reaction would succeed. The specification suggests that 100  $\mu$ M are used (Specification, page 8, line 9.) It is also recommended that the inhibitor and enzymes to be used as well as the amounts thereof be better defined and at least the amount of enzyme be defined with a phrase, such as, --in an effective amount of ... to prepare homogenisate--.

Claim 1 is confusing in the recitation of “said method is carried out”, since the antecedent basis is unclear. Also, it cannot be readily ascertained whether the inhibitor is present in a one pot reaction or whether the inhibitor is added to one or both of two separate reactions in two separate vessels.

Claim 12 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. It is apparent from claim 1 that the reactions are carried out in the same reaction vessel.

Claim 13 is vague and indefinite in the recitation “or alternatively they can be produced in situ by suitable biological organisms”. It is recommended that “are produced” be substituted for “can be produced”. Also the phrase “biological organisms” appears redundant. From the context of a “suitable reaction medium”, it appears that the proper term should be “suitable microorganisms”, since organisms such as animals appear excluded by the claims. See also Specification, page 4.

Claims 1-8 and 12-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Suemori *et al.* (1995) taken with Blakley *et al.*, Suemori *et al.* (1996) and Hareland *et al.*.

Suemori *et al.* (1995) discloses the enzymatic bioconversion of 4-hydroxyphenylpyruvate (HPP) into 4-hydroxyphenyl acetate and the enzymatic bioconversion of 4-hydroxyphenyl acetate (HPA) into homogentisate (HMO), using *R. erythropolis*. See, e.g., page 35. That the strain uses HPP or HPA as the sole carbon source is taught on page 33, last paragraph. In addition, Blakley *et al.* teach the enzymatic bioconversion of 4-hydroxyphenylpyruvate (HPP) into 4-hydroxyphenyl acetate using an enzyme produced by *Arthrobacter*, which grows on HPP as the sole carbon source. (See, e.g., bridging paragraph between col. 1-2, page 1129), and Suemori *et al.* (1996) and Hareland *et al.* teach the enzymatic bioconversion of 4-hydroxyphenyl acetate (HPA) into homogentisate (HMO), using *Pseudomonas acidovorans*, for example. (See, e.g., Suemori *et al.* (1996), page 133-134, and Hareland *et al.*, page 273.

Regarding inhibitors, Hareland *et al.* discusses HPP oxidase inhibitors at page 279, Figure 7. Clearly some activity remains in every instance, even though relatively high concentrations of inhibitors are used, i.e., 10-100 mM (page 278) and 165-660  $\mu$ M (page 279) rather than 100  $\mu$ M as used herein.

Accordingly, one of ordinary skill in the art would have had a reasonable expectation of success of using the teachings of the references to bioconvert 4-hydroxypyruvate enzymatically to homogentisate, even in the presence of an HPPD inhibitor, as adequately demonstrated by Hareland *et al.*.

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to modify the process of Suemori *et al.* (1995) by using further enzymes from other microorganisms for the hydroxypyruvate (HPP) into 4-hydroxyphenyl acetate and the enzymatic bioconversion of 4-hydroxyphenyl acetate (HPA) into homogentisate (HMO), in the presence of an HPPD inhibitor for the expected benefits of maximizing the yield of this valuable compound useful in a variety of pharmaceutical and industrial applications.

Thus, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary.

#### ***Response to Arguments***

Applicant's arguments have been fully considered but they are not deemed to be persuasive.

In response to applicant's arguments that none of the references discloses or suggests the claimed method it is noted that the enzymatic production of homogentisate by microbial enzymes is old and well known. With respect to the addition of an inhibitor to the reaction, Hareland *et al.* discusses the effects of HPP dioxygenase inhibitors as well as the presumed mechanism of the reaction to produce homogentisate (See, e.g., page 283). Inasmuch as the reference discloses that inhibitors vary in their effectiveness and that the effects are dependent on concentration, one of ordinary skill in the art would have had a reasonable expectation of success of carrying out the reaction in the presence of an HPPD inhibitor. The reference also suggests that inhibition of oxidase activity is desirable in the statement that the establishment of stoichiometry in the reaction of HPA to homogentisate was hindered by the presence of an oxidase (See, e.g., page 272, last paragraph. Thus, the reference provides compelling motivation for the addition of an inhibitor to the reaction to inhibit this activity.

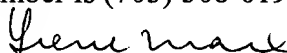
Therefore the rejection is deemed proper and it is adhered to.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Irene Marx whose telephone number is (703) 308-2922. The examiner can normally be reached on Monday through Friday from 6:30 AM to 3:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn, can be reached on (703) 308-4743. The appropriate fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to Customer Service whose telephone number is (703) 308-0198 or the receptionist whose telephone number is (703) 308-1235.

  
Irene Marx  
Primary Examiner  
Art Unit 1651